Top-down or step-up treatment in Crohn's disease?

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Abstract: In recent years, a change in the treatment goals for patients with Crohn's disease (CD) has come under intense discussion. Whereas 10 years ago treatment was initiated mainly in reaction to acute flares of the disease aimed to improve clinical symptoms, the focus now has changed to the prevention of damage to the intestinal wall. The prevention of structural damage by achievement of 'mucosal healing', however, is associated with the more 'aggressive' treatment and an earlier use of immunosuppressants and biologicals. The use of immunosuppressants and biologicals especially in patients with CD has decreased the rates of surgery and hospitalizations, indicating that there is a group of patients definitely profiting from such an early use of immunosuppressive treatment. In this group of patients, the benefits outweigh the disadvantages of immunosuppression: the increased risk of severe infections. However, it remains questionable whether this improvement can only be achieved by completely reversing established treatment strategies. The dispute has been condensed to the questions whether 'top-down' (e.g. start with a combination of biological and immunosuppressant and 'de-escalate' if possible) or 'step-up' treatment (e.g. start with topical steroids, step up to systemic steroid, go to immunosuppression and biologicals if necessary) may be better. In general, in an upcoming era of individualized and personalized medicine, a 'one-size-fits-all' approach does not appear to be desirable. CD patients definitely should not be undertreated (which is still frequently the case) or remain on steroid treatment (which is inappropriate); however, overtreatment (putting patients at risk of side effects without benefit) is against a fundamental principle of medicine: nihil nocere (do no harm).

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Top down or step up in Crohn's disease?

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Competing Interest

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Abbreviations: AZA: azathioprine; CD: Crohn's disease; CDAI: Crohn's disease activity index; IBD: inflammatory bowel disease; 6-MP: mercaptopurine; 6-UC: ulcerative colitis.

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Abstract

In recent years a change in the treatment goals for patients with Crohn's disease (CD) is under intense discussion. Whereas ten years ago treatment was initiated mainly in reaction to acute flares of the disease aimed to improve clinical symptoms the focus now has changed to the prevention of damage to the intestinal wall. The prevention of structural damage by achievement of "mucosal healing", however, is associated with the more "aggressive" treatment and an earlier use of immunosuppressants and biologicals. The use of immunosuppressants and biologicals especially in patients with CD has decreased the rates of surgery and of hospitalizations indeed indicating that there is a group of patients definitely profiting from such an early use of immunosuppressive treatment. In this patients group the benefits outweigh the disadvantage of immunosuppression: the increased risk of severe infections.

However, it remains questionable whether this improvement can only be achieved by completely reversing established treatment strategies. The dispute has been condensed to the questions whether "top down" (e.g. start with a combination of biological and immunosuppressant and "de-escalate" if possible) or "step up" treatment (e.g. start with topical steroids, step up to systemic steroid, go to immunosuppression and biologicals if necessary) may be better.

In general in an upcoming era of individualized and personalized medicine a "one fits all" approach appears not to be desirable. CD patients definitely should not be undertreated (which is still frequently the case) or remain on steroid treatment (which is inappropriate), however, overtreatment (putting

patients at risk of side effects without benefit) is against a fundamental principle of medicine: nihil nocere.

What does "step up" mean CD therapy?

Usually the term of "step up" treatment in CD refers to a more traditional approach of therapy: For a newly diagnosed patient suffering from CD first an approach is used that has a relatively lower risk of (severe) side effects. The choice of therapy is based on "the balance between drug potency and potential side-effects; previous response to treatment … and the presence of extraintestinal manifestations or complications" as stated in the ECCO guidelines [1].

As obvious from Cochrane reviews and meta-analyses the benefit of sulfasalazine and 5-aminosalicylic acid (5-ASA) preparations in uncomplicated CD is quite limited [2-4]. In a meta-analysis of three double-blind, randomized studies on the role of 5-ASA in the treatment of active CD 4 g/day 5-ASA were superior to placebo in reducing the CDAI, however, the clinical effect was not convincing [4,5]. Nevertheless, even new treatment guidelines still suggest to test a short course of sulfasalazine in colonic CD and do not exclude 5-ASA use in mild ileocecal disease ("The benefit of mesalazine is limited") [1] . In population based studies such as the IBSEN cohort there is a significant amount of CD patients that only received treatment with 5-ASA and never needed steroids [6,7]. Interpretation of those data is debatable.

There is better evidence for the use budesonide in mild to moderate flares of CD as the next step of treatment [1,8-11]. 9 mg budesonide per day is

effective and superior to treatment with 5-ASA [1,8] for the induction of remission in CD patients. Budesonide will induce remission in 51-60% of the patients within 8-10 weeks [1,8-11]. Mucosa healing is achieved only in 24% of treated patients [12]. The treatment is associated with limited side effects. Typical glucocorticoid associated side effects are less frequent as compared to systemic glucocorticoid treatment [9,11,13-15]. In patients with high disease activity and/or combined disease location in ileum and colon 18 mg budesonide per day are more effective; however more frequently systemic side effects become apparent [16].

In more severe disease the next step up would be the administration of systemic glucocorticoids. By a prednisone/prednisolone treatment with 100 mg/day in up to 92% of the patients remission can be achieved within 6 weeks [17,18].

In a systematic Cochrane review on the efficacy of conventional corticosteroids the authors identified two studies that compared corticosteroids to placebo and six studies that compared corticosteroids to 5-ASA [18]. Corticosteroids were found to be significantly more effective than placebo at inducing remission in CD [18]. In the short term intervention with steroids the number of adverse events did not differ between the glucocorticoids and high-dose 5-ASA [18]. Furthermore, glucocorticoids were not associated with more study withdrawals due to adverse events than placebo or 5-ASA [18]. This indicates that steroids are relatively save and well tolerated for the treatment of acute flares of CD.

In a “classical step-up approach” in patients not responding to steroids (steroid-refractory) or in which steroids cannot be tapered (steroid-

dependent) immunosuppressants (azathioprine; 6-mercaptopurine; methotrexate) or biologics (infliximab, adalimumab, certolizumab pegol) may be used [1]. Azathioprine (2-2.5 mg/kg body weight/day) and/or 6-mercaptopurine (1.0-1.5 mg/kg body weight/day) have been shown to be effective immunosuppressants in IBD [19]. Near complete mucosa healing has been reported in up to 83% of patients [12]. Methotrexate (MTX) is a suitable alternative (25 mg parenterally/once weekly) [20].

If a rapid treatment response is desired or if no remission can be achieved with azathioprine/6-marcaptopurine/methotraxte treatment with antibodies against tumor necrosis factor (infliximab, adalimumab, certolizumab) is associated with a success rate in up to 60-70% of the patients [21-25]. About 60% of the patients, who responded initially will achieve long-term remission [26-29]. There is a certain rate of secondary loss of response that is similar for all anti TNF products [30-35]. The different antibodies differ slightly in their therapeutic efficacy [36].

In contrast to studies that are based on single center experience or data from large hospitals in population based cohorts around 50% of patients with CD are reported to have been treated with corticosteroids [37]. In a population based cohort from Olmsted county it was reported that more than 1/3 of CD patients achieved remission with a treatment “one step below” systemic glucocorticoids [37]. This indicates that a group of CD patients (which may usually not be seen at referral centers) requires only mild therapy. From several population based cohorts (Olmstead county, IBSEN) it may be concluded that 30% -50% of patients will require immunosuppression. Of those about 50% or 15% - 25% of the total CD population will not be

sufficiently treated with purine analogs [38,39]. These patients will to step up to anti-TNF therapy.

What does "top down" mean in CD therapy?

The term "top down" in the context of CD therapy means that biologicals and immunosuppressants are applied right after the diagnosis of CD as a first line therapy. The "character" of the disease (whether it is mild disease with low activity and infrequent flares or vice versa aggressive disease with frequent flares or chronic active inflammation) is not further evaluated as this would further require some weeks or months.

The rationale for such an approach comes from rheumatology where an early intervention with biologicals is thought to be "disease modifying" e.g. preventing progressive destruction of joints [40]. In reality of course not all rheumatologic patients are treated top down.

With the top down approach one important questions remains: What can we do with the 40% of patients that don't come into remission as we know from the SONIC study [41] and other trials, so called "primary non-responders" [27,42]. The use of a second or even a third anti-TNF drug may eventually be effective [43,44], however, patients failing a first anti-TNF antibody are less likely to achieve remission with a second anti-TNF agent [43,Allez, 2010 #24065]. Another arising question is how to maintain remission in those patients. In the STORI trial a stopping strategy and criteria for therapy discontinuation have been provided [45]. In a prospective approach in 115 patients with CD that had been treated for at least one year with infliximab and thiopurines and had been in remission for more than six months,

infliximab was stopped and thiopurine therapy maintained [45]. The relapse rate after one year was reported to be 44%. Risk factors for a relapse were increased leukocyte counts, decreased hemoglobin levels, increased CRP and fecal calprotectin as well as absence of mucosal healing [45]. In the patients experiencing a relapse re-treatment with infliximab was effective in 88% [45]. Whereas it is now generally accepted that anti-TNF therapy should be administered on a regular basis ("scheduled treatment") as this reduces the risk for the formation of neutralizing antibodies, loss of response and allergic reactions unfortunately in the "top down – step up" study by D'Haens and coworkers infliximab was given more or less "on demand" after induction therapy [46].

Unfortunately the "step up" and "top down" approach are frequently discussed as exclusive alternatives indicating that either the one or the other strategy should be followed. In contrast it appears to be reasonable to identify a population that is at high risk of a severe and damaging disease course that will profit from a more aggressive approach with high probability. For those patients the risk/benefit ratio certainly would indicate a benefit for "top down" in the long run whereas for a CD patient population with mild disease course and low risk of complications the risk/benefit ratio will have an imbalance to the risk side. It is further of negative impact on this discussion that even in manuscripts that favour "top down" therapy only for such a risk populations general assumptions on CD are made (e.g. the contentional "step up" treatment approach does not alter the natural history of the disease – which obviously is wrong as the "natural" history

would be without intervention) that indicate an advantage of “top down” for the whole CD patient population

What assumptions are the bases of the discussion of “top down” versus “step up”?

What are the assumptions put forward to support a top down approach in CD therapy? The most important assumptions made in favor of a top down approach are depicted in table 1. It is stated that top down treatment is disease modifying, meaning that the “natural course” of CD is changed. It may be argued that any therapy will change the “natural course” of a disease if “natural” means the disease course without any intervention. It is obvious that some difficulties in the interpretation of the assumption that top down treatment is disease modifying is caused by the unclear meaning of “natural” disease course. The term has been adopted from rheumatology. However, even in rheumatology non-biological therapy may also prevent joint destruction to some extent. A further argument for a top down approach is that top down treatment induces more frequently mucosal healing. If compared with other drugs this is certainly the case. Obviously top down has the highest chance of inducing mucosal healing. But – still we are far from achieving mucosal healing in the majority of initially treated patients. Being “better” still could mean that an attempt to achieve mucosal healing can be undertaken with other drugs but in case of failure it may be switched to a biological. This is currently investigated in the CALM trial, which is a

very important clinical study. Achieving more often mucosal healing subsequently is not a very good argument for a top down approach. The next argument for a top down approach is that top down treatment induces long term remission. This, however, would only be a relevant argument if the same combination of drugs (i.e. biologicals and immunosuppressants) would not achieve long term remission in a step up approach. A final argument for top down is that step up treatment has significant disadvantages such as more days off work and more days of physical impairment and reduced quality of life.

Those arguments of course are to some extend interrelated and not completely separate or different. If the top down treatment induces more frequently mucosal healing then it will likely be associated with better remission rates and better long term remission. A CD patient in long term remission will experience less intestinal damage. So this indeed would be of great influence on the disease course.

Pariente has summarized this concept in an intriguing graph (Figure 2) [47]. If we only monitor clinical activity of CD (as it is still recommended in many guidelines), there may be sub-clinical disease activity causing damage to the intestinal mucosa or the intestinal wall. In Pariente's and coworkers original figure surgery always caused more damage to the gut indicating that it should be avoided under any circumstances [47]. Clinical reality argues against that. Only major resective surgery will cause additional damage to the intestine. Stricturoplasty or small resective surgery, fistula surgery, or abscess drainage will improve intestinal function and reduce the "digestive damage". We need to be fair with our surgical colleagues at that point.

Therefore, it is necessary to modify this scheme to better reflect clinical reality (Figure 2).

What evidence do we have to support a "top down" approach?

There are some good arguments for an early use of immunosuppressants or biologicals in a subgroup of CD patients. Most of the arguments, however, are of indirect nature.

- **Indirect evidence**

With respect to clinical remission subjects randomized to adalimumab in CHARM who enrolled in ADHERE were analyzed in an intention to treat (ITT) approach with respect to treatment efficacy in relation to disease duration [48]. The analysis was strict as subjects who moved to open label therapy in CHARM were classified as non-remitters from that point forward [48]. Subjects who moved to every week therapy during ADHERE were also classified as non-remitters from that point forward. Furthermore, missing data were classified as non-remission. With those strict criteria patients with a CD duration of less than two years achieved a remission in 55% 58 weeks after CHARM baseline, whereas only 40% or less of patients that suffered from CD for 2-5 years or more than five years were in remission (CDAI < 150) [48]. This difference was still obvious after 164 weeks after CHARM baseline, but less pronounced [48].

Besides clinical remission rates mucosal healing has been analyzed in detail. In the SONIC trial early anti-TNF-based therapy was associated with

sustained steroid-free remission and complete mucosal healing [41]. In SONIC azathioprine was compared to infliximab and the combination of both, a situation that cannot be directly compared to a top down versus step up situation.

In the above mentioned top-down vs. step up study by D'Haens and colleagues clinical remission rates were similar at week 104, but mucosal healing rate was higher with early anti-TNF therapy as compared to step-up therapy [49]. In those patients mucosal healing was a strong predictor of steroid-free remission [49]. In the STORI study performed by the GETAID mucosal healing predicted maintenance of clinical remission when anti-TNF therapy was discontinued [45]. In the EXTEND trial early anti-TNF use was associated with higher rate of mucosal healing than later use [50]. This is in line with earlier reports indicating that anti-TNF antibodies induce more effectively mucosal healing as compared to steroid therapy or immunosuppression [51-53]. Patients achieving mucosal healing have better long-term disease courses in population based cohorts. s seen in the IBSEN study [6].

Direct evidence

One of the first trials investigating early treatment of IBD was the Markowitz trial in pediatric patients who received 6-mercaptopurine (6-MP) right after the diagnosis of IBD [54]. In a prospective, placebo-controlled, multicenter trial the combination of 6-MP (or placebo) and prednisone as therapy for 55 children with newly diagnosed moderate-to-severe CD was evaluated. In the 6-MP group, the duration of steroid use was significantly shorter and the

cumulative steroid dose significantly lower. Remission was induced in 89% of both groups, but only 9% o 6-MP group relapsed compared as with 47% of placebo controls [54]. Markowitz and colleagues concluded that earyl immunosuppression with “6-MP should be part of the *initial* treatment regimen for children with newly diagnosed moderate-to-severe CD” [54] which reflects a top down approach.

The most important argument for a top down treatment is the clinical trial published by D’Haens and colleagues in Lancet [46]. They assessed the success rates of a top down versus a step up therapy in “newly diagnosed” CD of less than four years duration (n = 129) [46]. The patients had to be naïve to immunomodulators and biologicals. The top down group (n = 65) received azathioprine and infliximab in weeks 0, 2 and 5 and then later on the anti-TNF in an “on demand” strategy. The step up group (n= 64) received as a first line therapy steroids, in a second step azathioprine or methotrexate and as third line therapy infliximab. The co-primary endpoints (CDAI < 150 AND no steroids AND no surgery) were significantly different for both groups at weeks 24 and 52, however, there was no difference on week 80 and 104 [46,49]. At the end of the observation period the relative amount of patients receiving infliximab did not significantly differ and was around 20% [46,49]. However, as by definition the amount of patients receiving immunosuppressants was up to 100% in the top down group whereas it was around 80% in the step up group indicating that in 20% of patients steroids induced a long lasting remission without further need of escalation of therapy [46,49].

Mucosal healing was significantly more frequent in the top down group in 71% of patients whereas it was only achieved in 30% of the step up patients.

Weighing the value of top-down therapy

The benefits of a top down approach according to the above mentioned data are rather clear. There seems to be a better maintenance of remission after achieving it. Bowel function is more rapidly improved which is associated with an earlier improvement of the quality of life (QoL). The earlier promotion of mucosal healing may prevent complications such as perforations and obstructions [55-57].

On the other hand there are also significant disadvantages of a top down approach if applied to all patients without selecting those at risk for a complicated disease course. There are significant side effects of a more aggressive therapy to consider. The costs raised by a top down approach for every CD patient would be significant and no health care system could cover such a strategy making it unrealistic at the end. The majority of patients may not require more potent treatment at least initially.

This in mind we also should consider the data from the Norwegian population-based IBSEN study [6]. The investigators identified four primary courses of CD, and asked 197 patients to identify which curve best matched their disease course over the 10 years since diagnosis [6]. As these four distinct disease courses suggest, no single management plan will suit all patients. CD management must therefore be tailored to the individual patient.

The IBSEN data study suggest that 43% of patients may have a mild disease course and not require intensive therapy [6]. However, the majority of patients is likely to have chronic disease and may benefit from early intensive management.

Would an "accelerated step up treatment" cause a disadvantage and damage to IBD patients?

A very important question with respect to a decision between the top down or step up approach is whether a step up approach would indeed mean a significant disadvantage for the patient as mentioned above. Cosnes and coworkers compared an accelerated step up care with early or immediate start of immunosuppressants ("early azathioprine, e-AZA, n = 66) with conventional step up therapy (n = 68) in patients with CD [58]. The randomized, open-label controlled trial was conducted in 24 centers between 2005 and 2010. The aim of this study was to compare the accelerated step-care strategy in patients with early CD and predictors of disabling disease (age at diagnosis < 40, steroid use at first flare, perianal disease) with conventional therapy using steroids for the flare. Interestingly (in contrast to the Markowitz study in children) early AZA use in patients at high risk for disabling disease had no significant impact on the subsequent three-year CD course [58]. 62% of those CD patients assigned to the on-demand AZA group required AZA after a median follow up of 5.6 months. No significant differences were found between the two groups with respect to time spent in remission. Among the patients receiving early AZA ("top down"), 29% required additional treatment with anti-TNF agents, similar to 26% in the

steroid first/on-demand group who needed additional anti-TNF treatment. There was a trend to higher rates of unplanned perianal surgery in the steroid treated patients. A similar trend was observed for intestinal surgery: 11% of those who received early AZA and 21% of patients who started with steroids in the “classical step-up” approach required intestinal surgery without statistical significance between the groups (which could indicate that the study has not been sufficiently powered). Crohn’s Disease Activity Index (CDAI) and scores CRP were not different between the groups [58].

The authors mention that conventional therapy could allow patient to be vaccinated before immunomodulator therapy [58]. Overall the step up approach (which still was an “accelerated” approach applying immunosuppressant after a first failed steroid course) had no significant disadvantage in this setting. It is important to note that the authors tried to select patients with early disease and high risk for complicated disease course. Nevertheless at the end of the study, more than one-third of the patients in the step-up group had not met criteria for requiring AZA [58].

Indirect evidence also comes from another study. Sorrentino and coworkers investigated whether infliximab, given not immediately after surgery to prevent recurrence of CD but immediately after detection of postoperative endoscopic recurrence could induce endoscopic remission at 54 weeks. 43 patients with ileocolonic CD and ileocecal resection were included and underwent colonoscopy 6 months after surgery. 24 out 43 patients had and endoscopic recurrence at 6 months. 13 were treated with infliximab out of which 54% achieved endoscopic remission at 54 weeks and none had clinical recurrence [59]. Again this study may be underpowered to detect a

disadvantage of the delayed therapy and the observation period may be too short. In the study reported by Regueiro and coworkers the rate of endoscopic recurrence at 1 year was only 9% (1 of 11 patients) [60]. This could indeed indicate a benefit from a “top-down” approach in this situation. However, at the moment we do not have the clear evidence indicating that “accelerated step-up” upon demand is of disadvantage even for patients at some risk for complicated disease course.

Summary

A significant number of patients would be over-treated if a top-down therapy approach would be recommend for all patients diagnosed with CD. This would put patients with a mild and uncomplicated disease course at an unnecessary risk for therapy side effects and complications. Furthermore, there is no scientific evidence that an “accelerated step up” treatment (within the first or the first two years of disease) is of any disadvantage for the CD patient that develops a more severe disease. Most post hoc analyses in the respective anti-TNF trials indicating a better treatment effect in “early” disease usually looked at a group that had the disease for 2 years or less [61].

In an area in which – with good reasons - we favour an individualized therapy as well as personalized medicine a top down approach for all CD patients is displaced. A “one-fits-all” therapy principle only reflects a non-personalized and non-individualized therapy approach. Either we are able to detect better predictors of CD disease course or we only apply a top down therapy to the patient group at high risk for complications. A step-wise (but

nevertheless rapid) therapy escalation can take individual patient preferences and needs into account. A timely progress from ineffective therapy to the next step of treatment is mandatory to avoid disadvantages. This needs to be based on up-to-date knowledge and clinical trials. Subsequently, a careful patient selection will certainly justify the top down approach in a subgroup of CD patients. However, the selection criteria need to be further investigated and improved.

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Figure Legends:

Figure 1: Need for therapies among CD patients in population based cohorts

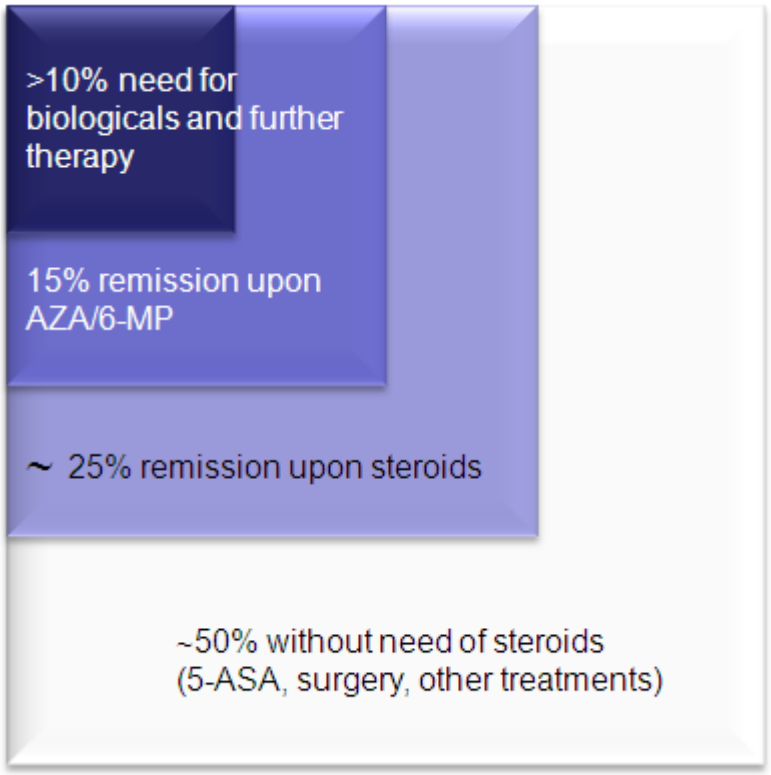

Figure 2: Disease courses in CD. Clinical activity may not reflect ongoing intestinal damage. Inflammation may be subclinical and result in cumulative tissue damage. Surgery may add additional tissue damage and loss of function or may restore function and reduce damage at least partially (modified according to [47]).

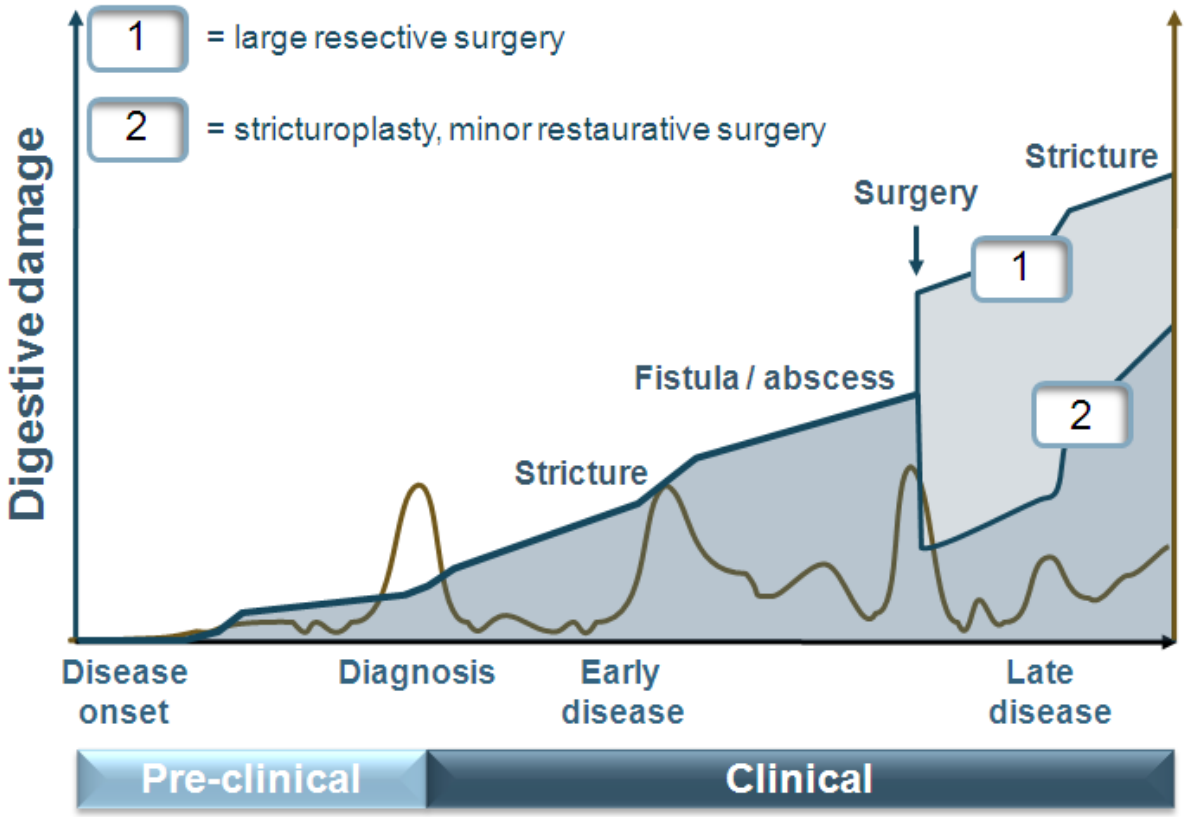

Table 1: Arguments for a top down treatment in patients with Crohn's disease

- Top down treatment is disease modifying
- Top down treatment induces more frequently mucosal healing
- Top down treatment induces long term remission
- Step up treatment has significant disadvantages